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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/559,327	04/27/2000	Mathew John During	40174	1919

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	12

DATE MAILED: 08/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/559,327	Applicant(s) DURING, MATHEW JOHN	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 April 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Non-Final Rejection

Claims 1-6, 8, and 10-12 are pending in this application.

Applicants' traversal in paper no. 11 is acknowledged and considered.

Drawings

NOTE: In the next response, please submit a response to the PTO 498 because a PTO 498 was filed with the non-final rejection dated 12/04/01 and the applicants have not submitted proposed corrections to the drawings. If the reply to the Non-Final Rejection does not have a response to the 498, the response will be considered non-responsive. See 37 CFR 1.85(a).

Claim Objections

Claim 2 is objected to because of the following informalities: Claim 2 is objected to for reciting a grammatically improper phase, "...vector is administered dissolved or suspended in a liquid ...". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8, and 10-12 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method of expressing a gene product in the gastrointestinal tract (GI) of an animal, which comprises: orally delivering an encapsidated recombinant AAV vector, wherein said vector comprises a gene encoding a protein; 2) The

method of 1, wherein said gene is operably linked to a promoter operable in said GI, 3) The method of 1, wherein said vector is dissolved or suspended in a liquid pharmaceutically acceptable carrier; and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention encompasses delivery of a recombinant adeno-associated virus comprising a heterologous gene, wherein expression of said gene is observed in the gastrointestinal (GI) tract of a mammal.

Furthermore, and with respect to claims directed to any vector (e.g. AAV) useful for gene therapy and directed to any treatment of a mammal; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

The disclosure teaches using an oro-gastric tube for delivering a recombinant AAV vector comprising a gene encoding β-galactosidase to a rat model of lactose intolerance, which

resulted in the phenotypic correction of rats with lactose intolerance (pages 14-17). The specification contemplates using pharmaceutical compositions for administering the AAV to an animal (page 10). The specification further contemplates that the AAV vector means a bare recombinant AAV vector or AAV vector packaged into a viral capsid (page 10). In addition, the specification cites Sandler et al. (Am. J, Clin. Nutr. 1985, Vol. 42, pp. 270-275), who teaches that AAV is resistant to temperature, pH extreme, and solvents (page 13). However, the article cited by the disclosure appears to discuss post-menopausal bone density and milk consumption in childhood and adolescence and evidence to the contrary does not discuss the resistant of AAV to severe conditions.

The specification provides sufficient guidance for one skilled in the art to orally administer an encapsidated AAV vector comprising a gene product into the gut of an animal for gene expression. However, it is not apparent from the as-filed specification, if the working examples used a bare recombinant AAV vector or AAV vector packaged into a viral capsid. The state of the art at the time the application was filed and currently for gene delivery was considered unpredictable as exemplified by Page et al., DDT, and Vol. 6, 2001, pages 92-101, Page teaches that:

> To date, most gene delivery strategies have concentrated on the parenteral route of delivery and oral administration has been largely ignored. This is mainly due to the large hurdles that need to be overcome for oral gene delivery, such as acid pH in the stomach, the nucleases, lipases, and the poor permeability of both genes and gene vectors across the intestinal epithelium owing to the size and charge of the gene delivery vehicles. As a result of these factors, the greatest challenge faced by oral gene therapy is achieving

delivery of sufficient genetic material in the correct cell types to produce therapeutic or prophylactic protein expression levels (page 92).

Furthermore, Page teaches:

Despite the fact that somatic gene therapy to the intestine was suggested in 1992, it has not been seriously investigated until recently. This was primarily because of the low oral bioavailability of the available DNA vector systems and also the relatively few genetic disorders directly associated with the GI tract (e.g. familial adenomatous polyposis, cystic fibrosis and various colon cancers. See page 93.

In view of the state of the art, the as-filed specification is only enabled for using an encapsidated AAV vector for gene expression in the gut of an animal because in view of the art of record and the lack of sufficient guidance provided by the as-filed specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from using an encapsidated AAV vector to the full breadth of the claims that encompass any recombinant AAV vector because of the anatomic and physiologic barriers of an animal, which include mucus (entraps foreign pathogens), gastric acidity, and interferons, to administer said vector to an animal. Furthermore, a naked AAV vector consists of DNA. In view of the concerns set forth by Page (e.g. low oral bio-availability of the available gene, acid pH in the stomach, nucleases, lipases, and poor permeability of both genes and gene vectors across the intestinal epithelium), a naked DNA would be degraded in the stomach due to the low pH in the stomach and because one skilled in the art understands that nucleases present in the stomach would destroy the DNA. The art of record and the as-filed specification do not provide sufficient guidance and/or factual evidence for how to avoid degradation of AAV vector (DNA vector) due to the presence of

nuclease (which is an enzyme that degrades DNA) in the stomach. In view of the doubts expressed in the art of record and the amount of direction or guidance presented by the specification, which fails to provide sufficient guidance for one skilled in the art to reasonably extrapolate from using an encapsidated AAV vector to using any other AAV vector (bare AAV vector). Therefore, in view of the art of record at the time the application was filed, the claimed invention is only enabled for using an encapsidated AAV vector for use in delivery of a gene product to the gut an animal, however delivering a bare AAV vector to the gut was considered unpredictable because of the large hurdles that need to be overcome for gene delivery to the gut of an animal.

As stated above, in view of the state of the art and the disclosure, the claimed invention is enabled for only using an encapsidated AAV vector for gene expression in the gut of an animal and not the full breadth of recombinant AAV vector. In addition, with respect with respect to claims 1-6, 8, 10-12, which encompass several routes of administration, especially intramuscular, intravenous, suppository because of the breadth of the claim, the disclosure in view of the In re Wands Factors, fails to provide sufficient guidance for any other route of administration other than using an oral administration of an encapsidated AAV vectors to a animal. For example, the as-filed specification fails to provide sufficient guidance how to reasonably correlate a method of orally administering encapsidated AAV to a method of expressing a gene product in the gut of an animal using any other route of administration because it is not apparent how intranasally, intravenously, suppository, etc. would result in gene product expression the gut. In addition, the as-filed specification only contemplates

oral administration and does provide sufficient guidance and/or factual evidence for any other route including intraperitoneal injection of any AAV vector. In view of the art of record and the lack of sufficient guidance provided by the as-filed specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from using oral administration to any other route of administration for expression of a gene product in the gut of an animal because of the anatomic and physiologic barriers of an animal, which include mucus (entraps foreign pathogens), gastric acidity, and interferons, to administer the AAV vector to an animal. In view of the doubts expressed in the art of record by Page and the amount of direction or guidance presented by the specification, which fails to provide sufficient guidance for one skilled in the art to reasonably extrapolate from using an oral administration to using any other route of administration of AAV vectors to an animal. At the time the application was filed, oral gene therapy was considered enabled for delivery to the gut an animal, however any other route of administration to the gut was considered unpredictable because of the large hurdles that need to be overcome for gene delivery to the gut of an animal.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable 1-3 listed above. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the application was filed, and given the lack of sufficient guidance as to a gene therapy effect produced by any AAV vector cited in the claims for treating any disorder or any disease that does require precise gene

regulation other than treating a mammal with any GI disorder or disease that does not require precise gene regulation, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

Applicant's traverse the rejection for pending claims under 112 enablement in paper no. 11. Applicant's traverse that: An oro-gastric tube does not run into the intestine; There is no mention on page 11 of the specification of using an oro-gastric tube; Thus, while a tube was used in the working examples, the instant specification teaches making ingestable forms of drug containing AAV; Page and Cudmore are no relevance the claimed invention because AAV is a very stable particle resistant to temperature and pH extremes as well as many solvents; A number of different ways for non-parenteral administration are taught by the specification (See page 9 of the as-filed specification). See pages 2-9.

Applicants' traversal is acknowledged and is found partially persuasive. The claimed invention is enabled for 1-3 listed above. However, the claimed invention is not enabled for the full scope of the claimed invention because of the unpredictability of gene therapy for orally delivering any bare AAV vector to the gut and/or using any other route of administration other than oral administration in view of the unpredictability of gene therapy.

Furthermore, to the extent that the applicant's traversal is applicable to any other route of administration, the traversal is not found persuasive because the as-filed specification only teaches how to use oral administration and this route does not reasonably extrapolate to the using any other route of administration because of the problems of using any route of administration other than oral administration for gene expression in the gut of an animal (See Anderson, Verma,

and Rubanyi). In addition, the state of the art at the time the application was filed and currently display that, "Information on the stability and persistence of macromolecules in the intestinal system has previously not been available (see Hohlweg et al. Mol. Genet. Genomics, Vol. 265, pp. 225-233, 2001)." Therefore, in view of the unpredictability of gene therapy and the lack of guidance and/or factual evidence provided by the as-filed specification and/or the applicants' traversal for using any route of administration other than using an oral, it would take one skilled in the art an undue amount to reasonably extrapolate from using an oral to using any other route of administration to deliver encapsidated AAV vector to the intestine of the mammal.

Furthermore, to the extent that the applicants' traversal is applicable to using a naked AAV vector, the traversal is not found persuasive because a naked AAV vector consists of DNA. In view of the concerns set forth by Page (e.g. low oral bio-availability of the available gene, acid pH in the stomach, nucleases, lipases, and poor permeability of both genes and gene vectors across the intestinal epithelium), a naked DNA would be degraded in the stomach due to the low pH in the stomach and because one skilled in the art understands that nucleases present in the stomach would destroy the DNA. The art of record and the as-filed specification do not provide sufficient guidance and/or factual evidence for how to avoid degradation of bare AAV vector (DNA vector) due to the presence of nuclease (which is an enzyme that degrades DNA) in the stomach. Therefore, in view of the unpredictability of gene therapy and the lack of guidance and/or factual evidence provided by the as-filed specification and/or the applicants' traversal for using any recombinant AAV vector other than an encapsidated AAV, it would take one skilled in the art an undue amount to reasonably extrapolate from using an encapsidated AAV to any other recombinant AAV vector for delivery to the intestine of the mammal via oral administration.

Double Patenting

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 10-11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 7, 19-20, and 42 of co-pending Application No. 09/510,144. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of co-pending application '144 are drawn to a method for delivering a protein to a gut tissue of a subject comprising orally delivering to the gut tissue an AAV vector.

Although the conflicting claims in the instant application and co-pending application '144 are not identical, they are not patentably distinct from each other because each invention encompasses the same material and methods and the co-pending claims a method of orally delivering a recombinant AAV vector to the gut of a subject. The difference between the claims of the instant application and co-pending application '144 is that the claims in the instant application are not as descriptive as the claims from the co-pending application '144. Therefore, the claims of the instant application and co-pending application '144 are obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

To the extent that the applicants' traversal is applicable to the rejections under double patenting, the traversal is not found persuasive for because it is not applicable to the rejection.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
8/12/02

DAVE T. NGUYEN
PRIMARY EXAMINER